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<p>(54) Title: A NEW SALT</p> <p>(57) Abstract</p> <p>A new salt (<i>R</i>)-3-<i>N,N</i>-dicyclobutylamino-8-fluoro-3,4-dihydro-2<i>H</i>-1-benzopyran-5-carboxamide hydrogen tartrate, particularly the (2<i>R</i>,3<i>R</i>)-tartrate thereof, most particularly the (<i>R</i>)-3-<i>N,N</i>-dicyclobutylamino-8-fluoro-3,4-dihydro-2<i>H</i>-1-benzopyran-5-carboxamide hydrogen (2<i>R</i>,3<i>R</i>)-tartrate monohydrate, processes for the manufacture of said tartrate salt, the use of the salt in medicine, the use of the tartrate salt in the manufacture of pharmaceutical formulations, and a method for the treatment of CNS disorders by administration of the tartrate salt to a host in need of such treatment.</p>			

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A new salt

### Field of the Invention

5 The present invention relates to a new salt, namely (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen tartrate, particularly the (2*R*,3*R*) form of the tartrate and most particularly the monohydrate thereof. The invention also relates to processes for the manufacturing of the salt, the use of the salt in the manufacture of pharmaceutical formulations, to the use of the salt in medicine and methods of  
10 treatment employing the salt particularly, in its monohydrate form.

### Background of the Invention

15 The compound (*R*)-5-carbamoyl-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran, which also may be named (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide and pharmaceutically acceptable salts thereof are described in WO 95/11891.

20 The disclosed hydrochloride salt of (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide is hygroscopic and thus physically instable during manufacturing as well as during storage.

### Disclosure of the Invention

25 It has now surprisingly been found that the salt (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen tartrate, particularly the (2*R*,3*R*) form of the tartrate, in the anhydrous form or as the hemihydrate or monohydrate is physically more stable during storage than the hydrochloride salt of said compound, since the tartrate  
30 forms of the compound are not disposed to absorb water to the same degree as the

hydrochloride salt of the same compound. This property of absorbing water is also a problem during storage and during manufacture of, e.g., solid pharmaceutical dosage forms such as tablets and hard gelatine capsules.

5 The good solubility and dissolution properties of the anhydrous tartrate salt are even more pronounced for the monohydrate of the tartrate salt, particularly the (2*R*,3*R*)-tartrate monohydrate. The water is firmly bound in the crystal lattice and is not released even upon heating up to 70 °C. This is well above the commonly used process temperatures, e.g., during the granulation process, in the production of tablets and hard gelatine capsules.

10 The good solubility and dissolution properties of the tartrate salt from, e.g., the oral drug delivery point of view, together with the low degree of hygroscopicity under normal humidity conditions makes the monohydrate form the most suitable form of the tartrate salt, and particularly the (2*R*,3*R*)-tartrate monohydrate from a quality assurance standpoint.

15 Thus, the monohydrate of (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate, has surprisingly been shown to be physically stable under normal humidity conditions. To be suitable for long term storage and is easier to work with in the production of different solid pharmaceutical dosage forms.

20 Accordingly, the present invention relates to the salt (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen tartrate, particularly to the salt (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate and more particularly to the salt (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate  
25 monohydrate.

The present invention includes (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen tartrate, in the form of (2*R*,3*R*)-tartrate, (2*S*,3*S*)-  
30 tartrate and (2*R*,3*S*)-tartrate.

The salts of the invention may be used as selective 5-HT<sub>1A</sub> receptor antagonists in the treatment of CNS disorders and related medical disturbances. Examples of such disorders are depression, anxiety, obsessive-compulsive disorder (OCD), anorexia, bulimia, senile dementia, migraine, stroke, Alzheimer's disease, cognitive disorders, schizophrenia, especially cognitive dysfunction in schizophrenia, sleep disorders, urinary incontinence, premenstrual syndrome, hypertension and pain. Examples of such medical disturbances are thermoregulatory disturbances, sexual disturbances, disturbances in the cardiovascular system and disturbances in the gastrointestinal system.

- 10 The novel salt (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen tartrate, particularly the (*2R,3R*) form of the tartrate and most particularly the monohydrate of said tartrate salt exists preferably in substantially crystalline form may be formulated into various dosage forms for oral, parenteral, rectal and other modes of administrations.
- 15 Examples of formulations are tablets, pellets, granules, capsules (e.g. hard gelatine capsules), aqueous solutions and suspensions.

Usually the active ingredient will constitute from 0.0001 to 99% by weight of the formulation, more preferably from 0.001 to 30% by weight of the formulation.

20

To produce pharmaceutical formulations containing the active ingredient of the invention in the form of dosage units for oral applications, one may mix the active ingredient with a solid excipient, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, a cellulose derivative, a binder such as gelatine or poly-vinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, sodium stearyl fumarate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. The active ingredient may be granulated together with excipients using an aqueous or organic solution of binders, and then dried and screened prior to tablet compression.

If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, e.g., gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet can be coated with a polymer known to a person skilled in the art, that is dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to readily distinguish between tablets containing different amounts of active ingredient.

For the preparation of hard gelatine capsules, the active ingredient may be processed in the form of granules, and may be admixed with the excipients mentioned above for tablets.

For the preparation of soft gelatine capsules, the active ingredient may be admixed with e.g. a vegetable oil or polyethylene glycol.

Suppositories for rectal administration may be prepared by dissolving or suspending the active ingredient in a molten suppository base such as Witepsol<sup>®</sup> followed by casting and cooling.

Gelatine rectal capsules may comprise the active ingredient in admixture with vegetable oil or paraffin oil and may contain some of the polymers and/or dyestuff mentioned above.

Aqueous solutions for parenteral or oral administration are produced by dissolving the active compound of the invention in water, adjusting the pH and ionic strength with common buffering agents such as citric acid, phosphoric acid or other similar acids or their commonly used salts; sodium carbonate, hydrogen carbonate or other similar salts; or hydrochloric acid or sodium hydroxide. In the case of parenteral solutions the sterility is ensured by final heat sterilization or, e.g., sterile filtration. Lyophilization, resulting in a reconstitutable solid product, may also be used.

Suitable daily doses of the salt of the invention in therapeutical treatment of humans are about 0.001-100 mg/kg body weight.

The specific processes for manufacturing (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (*2R,3R*)-tartrate, (*2S,3S*)-tartrate or (*2R,3S*)-tartrate, respectively, more specifically the monohydrate thereof, are a further aspect of the invention.

5

The process for manufacturing the new salt form (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (*2R,3R*)-tartrate, more specifically the monohydrate thereof, comprises the following consecutive steps:

- 10 i) dissolving (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide in an appropriate organic solvent, optionally by heating,
- ii) adding (*2R,3R*)-tartaric acid dissolved in an appropriate aqueous organic or non-aqueous organic solvent,
- 15 iii) allowing the obtained solution to stand cold in order to crystallize,
- iv) optionally, recrystallizing from an aqueous organic solvent, if a non-aqueous organic solvent is used in step ii), to obtain the tartrate monohydrate salt.

20

The corresponding (*2S,3S*)-tartrate and (*2R,3S*)-tartrate compound are manufactured by using (*2S,3S*)-tartaric acid and (*2R,3S*)-tartaric acid, respectively in step ii) above.

25

A more detailed description of the process of manufacturing is presented in Examples 1 and 2.

Starting from the anhydrous form or a mixture of the anhydrous form and the hemihydrate of (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (*2R,3R*), (*2S,3S*) or (*2R,3S*)-tartrate, obtained by any suitable process,

recrystallization of the said tartrate from an appropriate aqueous organic solvent will give the monohydrate of the invention.

Appropriate solvents for dissolving (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-  
5 2*H*-1-benzopyran-5-carboxamide may be organic solvents such as tetrahydrofuran, diethyl ether, acetone, ethanol, methanol and other alcohols.

Appropriate aqueous organic solvents used in the crystallization or recrystallization may be alcohols, nitriles, esters, or ketones e. g. methanol, ethanol, isopropanol, acetonitrile, or  
10 acetone, preferably acetone.

### Example 1

#### **(*R*)-3-*N,N*-Dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide Hydrogen (2*R*,3*R*)-Tartrate**

(*R*)-3-*N,N*-Dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide (100 mg, 0.31 mmol) was dissolved in tetrahydrofuran (1 mL) by heating and the solution was  
20 diluted with diethyl ether (25 mL). To this solution was added a solution of (2*R*,3*R*)-tartaric acid made by dissolving 55 mg (0.35 mmol) of (2*R*,3*R*)-tartaric acid in tetrahydrofuran (1 mL) and diluting with diethyl ether (25 mL). The milky solution obtained was filtered and allowed to stand in the refrigerator overnight. The solid was filtered and dried in a vacuum oven to give the title compound in 142 mg white crystals  
25 (98% yield). Mp 174-180°C (DSC). Anal. Calcd. for C<sub>22</sub>H<sub>23</sub>FN<sub>2</sub>O<sub>8</sub>: C, 56.4; H, 6.2; N, 6.0. Found: C, 56.2; H, 5.9; N, 5.6.



**Example 2****(R)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide  
Hydrogen (2*R*,3*R*)-Tartrate Monohydrate**

5

(*R*)-3-*N,N*-Dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide (2.0 g, 6.3 mmol) was dissolved in tetrahydrofuran (5 mL) by heating and the solution was diluted with diethyl ether (400 mL). To this solution was added a solution of (2*R*, 3*R*)-tartaric acid made by dissolving 1.1 g (6.9 mmol) of (2*R*, 3*R*)-tartaric acid in  
10 tetrahydrofuran (15 mL) and diluting with diethyl ether (300 mL). The clear solution obtained was allowed to stand in the refrigerator over the weekend. The crystalline solid obtained was filtered and recrystallized from 1.5% aqueous acetone (400 mL) to give of the title compound 2.6 g sparkly crystals (85% yield). Mp. 174-180°C (DSC). Anal. Calcd. for C<sub>22</sub>H<sub>25</sub>FN<sub>2</sub>O<sub>9</sub>: C, 54.3; H, 6.4; N, 5.8. Found: C, 54.4; H, 6.3; N, 5.6.

15

**Analytical test method used on the products obtained in Examples 1 and 2**

The melting point (Mp) was measured by using differential scanning calorimetry (DSC).

20

**Establishment of water content****a) Thermogravimetric assay**

Thermogravimetric measurements performed showed that the anhydrous form of (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen  
25 (2*R*,3*R*)-tartrate obtained in Example 1 had an initial weight loss of 0.997% w/w. The initial weight loss of 4.104% w/w for the monohydrate of (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate obtained in Example 2 compared favourably with the theoretical water content of a  
30 monohydrate.

## b) X-Ray Diffraction

X-ray intensity data were collected on a single-crystal *MACH3/CAD4* diffractometer (Enraf-Nonius, 1994) equipped with graphite monochromatic  $\text{CuK}(\alpha)$  radiation and a proportional scintillation counter. The structure was solved by direct methods, *SIR92* (Altomare, Cascarano, Giacovazzo & Guagliardi, 1992) and refined with full-matrix least-square methods, *LSFM* (Hansen & Coppens, 1974), within the *MolEN* software package (Straver & Schierbeck, 1994). All non-hydrogen atoms were refined anisotropically, whereas hydrogen atoms not involved in short intermolecular contacts were fixed from a late difference Fourier and supplied with isotropic displacement parameters,  $U_{\text{iso}} = 0.06 \text{ \AA}^2$ . Hydrogen atom positions involved in H-bonding were refined freely and assisted with a fixed isotropic temperature factor,  $U_{\text{iso}} = 0.06 \text{ \AA}^2$ , except for the crystal water hydrogens for which the factor used was  $U_{\text{iso}} = 0.07 \text{ \AA}^2$ .

Figure 1 shows the three-dimensional structure and absolute configuration of (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide in relationship to the (2*R*,3*R*)-tartrate portion and the water molecule.

### Determination of stability

Moisture sorption of the monohydrate of (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate compared to that of the anhydrous form of (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate, as well as to that of the HCl-salt has been set as a measure of the relative physical stabilities of the respective products.

The moisture sorption analysis, absorption and desorption, respective was performed using a VTI microbalance, Model MB300W (VTI Corporation, USA) linked to an IBM PC. The relative humidity (RH) within the balance was monitored using a dew point analyser.

Approximately 10 mg of substance was dried to constant weight at 60°C and then exposed

stepwise to RHs of from 5 to 90% at 25°C, the step interval being 5%. The desorption profile was also obtained.

Figure 2 shows the moisture sorption curve of the HCl salt of (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide. As seen from the figure, the HCl salt takes up a considerable amount of moisture at high relative humidities. At 85% relative humidity the HCl salt has taken up approximately 20% w/w and exhibits deliquescence.

Figure 2 also shows the moisture sorption curve of the anhydrous form (anhydrate) of (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate. As seen from the figure, the anhydrous form (anhydrate) absorbs moisture readily. At a RH of 90%, about 4.2 % (w/w) moisture was absorbed. The desorption profile (the upper part of the curve) indicates that the moisture taken up is firmly bound and that the sample has formed a monohydrate.

Figure 2 shows the moisture sorption curve of the monohydrate of (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate. As seen from the figure the monohydrate absorbs only 2.5% (w/w) at 90% RH. Significant uptake of moisture was only recorded at RH of approximately 60% or above. The desorption profile shows that the moisture uptake is reversible.

## CLAIMS

1. A salt (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen tartrate.

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2. A salt (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate.

10

3. The salt (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate.

4. The salt according to any one of claims 1 to 3 in substantially crystalline form.

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5. A pharmaceutical formulation containing, as active ingredient, the salt according to any one of claims 1 to 4 in association with a suitable diluent, excipient or an inert carrier.

6. A pharmaceutical formulation according to claim 5 for oral administration.

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7. The salt according to any one of claims 1 to 4 for use in therapy.

8. The use of the salt according to any one of claims 1 to 4 in the manufacture of a medicament in the prevention or in the treatment of CNS disorders and related medical disturbances.

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9. The use according to claim 8 in the manufacture of a medicament in prevention or in the treatment of 5-HT<sub>1A</sub> receptor antagonist activity related CNS disorders and medical disturbances.

10. The use according to claim 9 in the manufacture of a medicament in the prevention or in the treatment of depression.
11. The use according to claim 9 in the manufacture of a medicament in the prevention or  
5 in the treatment of anxiety.
12. A method for the prevention or the treatment of CNS disorders and related medical disturbances comprising administration, to a host in need of such treatment, an effective amount of the salt according to any one of claims 1 to 4.
- 10 13. A method according to claim 12 for prevention or the treatment of 5-HT<sub>1A</sub> receptor antagonist activity related CNS disorders and medical disturbances.
14. A method according to claim 13 for the prevention or the treatment of depression.
- 15 15. A method according to claim 13 for the prevention or the treatment of anxiety.
16. A process for the manufacture of the salt as defined in any one of claims 1 to 4 characterized by the following consecutive steps:
- 20 i) dissolving (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide in an appropriate solvent, optionally by heating,
- ii) adding (*2R, 3R*)-, (*2S, 3S*)- or (*2R, 3S*)-tartaric acid, respectively, dissolved in an  
25 appropriate aqueous organic solvent or non-aqueous organic solvent,
- iii) allowing the solution obtained to stand cold to crystallize,

iv) optionally recrystallizing in an appropriate aqueous organic solvent, if a non-aqueous organic solvent is used in step ii), to obtain the salt defined in any one of claims 3 or 4.

- 5 17. A process for the manufacture of the salt as defined in claims 3 to 4 characterized by recrystallizing (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3, 4-dihydro-2*H*-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-, (2*S*,3*S*)- or (2*R*,3*S*)-tartrate in an appropriate aqueous organic solvent.
- 10 18. A process according to any one of the claims 16 or 17, wherein the aqueous organic solvent is aqueous acetone.

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## AMENDED CLAIMS

[received by the International Bureau on 17 September 1998 (17.09.98);  
original claims 1-18 replaced by amended claims 1-17 (2 pages)]

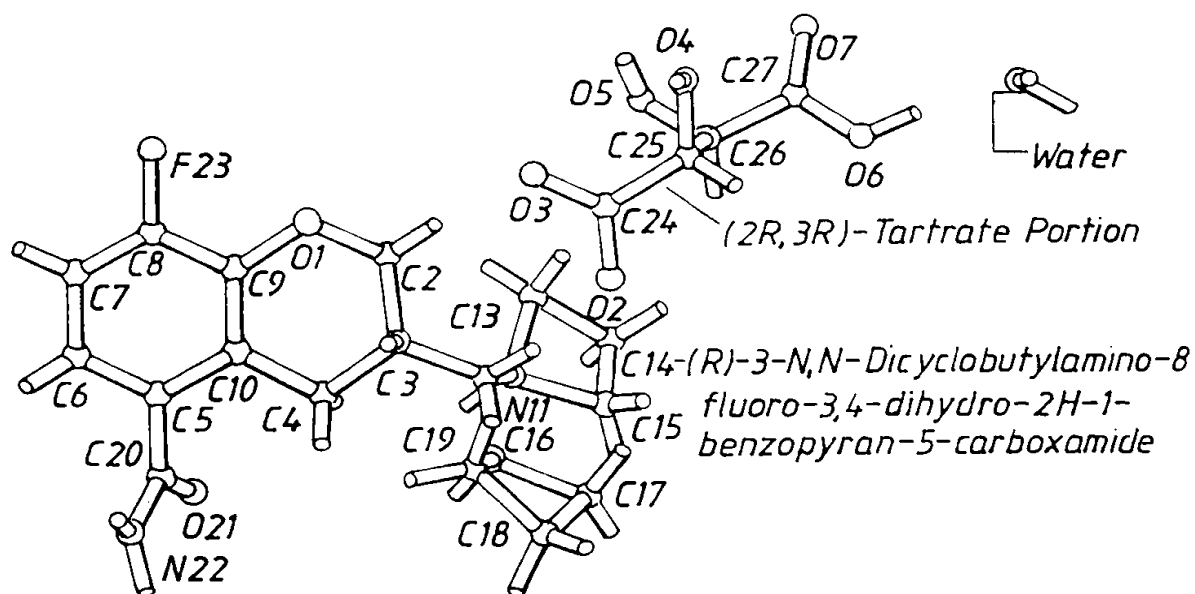
1. A salt (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate.  
5
2. The salt (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide hydrogen (2*R*,3*R*)-tartrate monohydrate.
- 10 3. The salt according to any one of claims 1 to 2 in substantially crystalline form.
4. A pharmaceutical formulation containing, as active ingredient, the salt according to any one of claims 1 to 3 in association with a suitable diluent, excipient or an inert carrier.
- 15 5. A pharmaceutical formulation according to claim 4 for oral administration.
6. The salt according to any one of claims 1 to 3 for use in therapy.
- 20 7. The use of the salt according to any one of claims 1 to 3 in the manufacture of a medicament in the prevention or in the treatment of CNS disorders and related medical disturbances.
8. The use according to claim 7 in the manufacture of a medicament in prevention or  
25 in the treatment of 5-HT<sub>1A</sub> receptor antagonist activity related CNS disorders and medical disturbances.
9. The use according to claim 8 in the manufacture of a medicament in the prevention or in the treatment of depression.
- 30 10. The use according to claim 8 in the manufacture of a medicament in the prevention or in the treatment of anxiety.
11. A method for the prevention or the treatment of CNS disorders and related medical  
35 disturbances comprising administration, to a host in need of such treatment, an effective amount of the salt according to any one of claims 1 to 3.

12. A method according to claim 11 for prevention or the treatment of 5-HT<sub>1A</sub> receptor antagonist activity related CNS disorders and medical disturbances.
13. A method according to claim 12 for the prevention or the treatment of depression.
14. A method according to claim 12 for the prevention or the treatment of anxiety.
15. A process for the manufacture of the salt as defined in any one of claims 1 to 3 characterized by the following consecutive steps:
- i) dissolving (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3,4-dihydro-2*H*-1-benzopyran-5-carboxamide in an appropriate solvent, optionally by heating,
  - ii) adding (*2R, 3R*)-tartaric acid, respectively, dissolved in an appropriate aqueous organic solvent or non-aqueous organic solvent,
  - iii) allowing the solution obtained to stand cold to crystallize,
  - iv) optionally recrystallizing in an appropriate aqueous organic solvent, if a non-aqueous organic solvent is used in step ii), to obtain the salt defined in any one of claims 2 or 3.
16. A process for the manufacture of the salt as defined in claims 2 to 3 characterized by recrystallizing (*R*)-3-*N,N*-dicyclobutylamino-8-fluoro-3, 4-dihydro-2*H*-benzopyran-5-carboxamide hydrogen (*2R,3R*)-tartrate in an appropriate aqueous organic solvent.
17. A process according to any one of the claims 15 or 16, wherein the aqueous organic solvent is aqueous acetone.



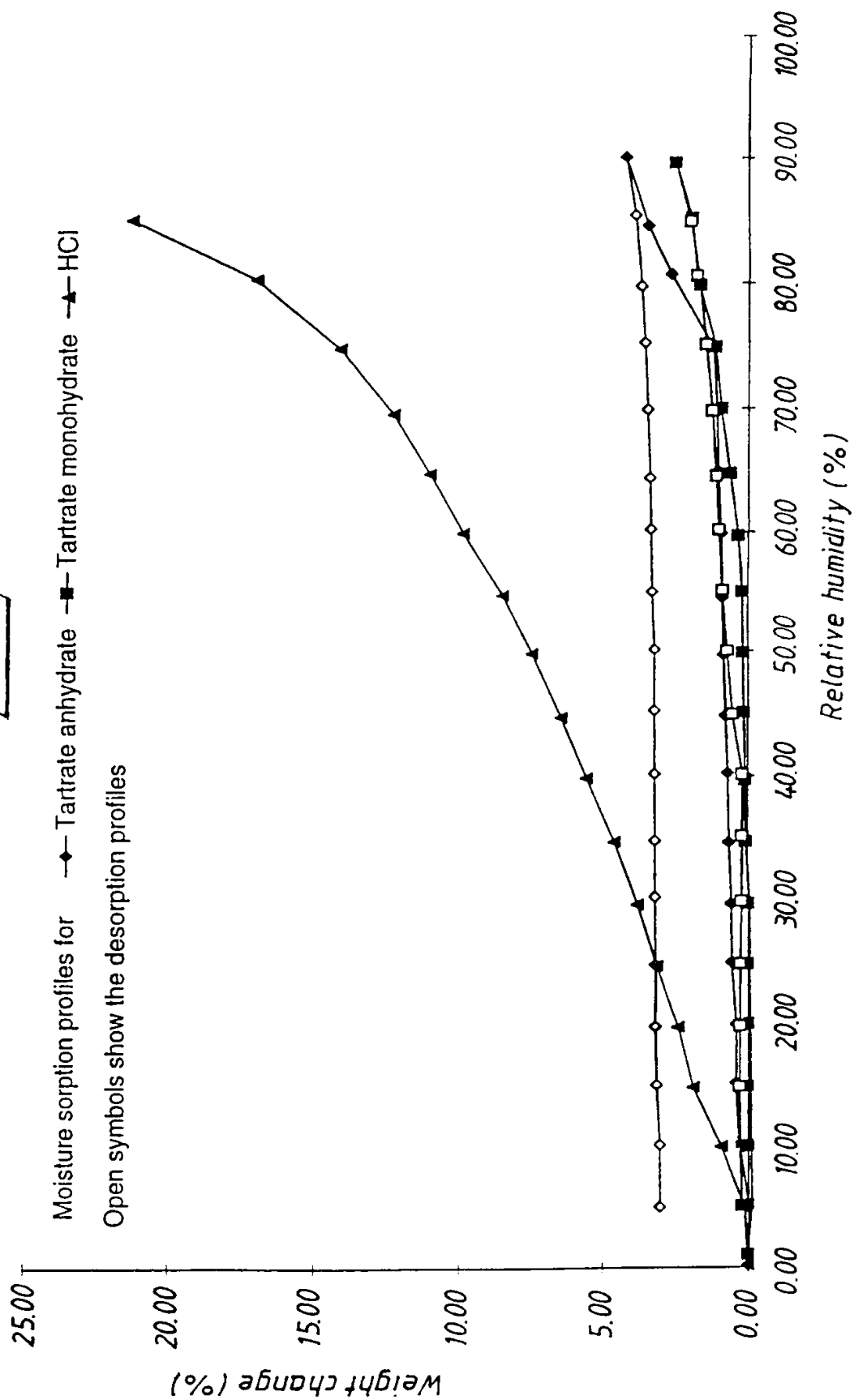
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Fig. 1



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Fig. 2



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00907

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 311/58, A61K 31/35

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9511891 A1 (ASTRA AKTIEBOLAG), 4 May 1995 (04.05.95)  -----	1-11,16-18

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

25 August 1998

Date of mailing of the international search report

07-09- 1998

Name and mailing address of the ISA /

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/00907

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12-15  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
A method for treatment of the human or animal body by therapy,  
see Rule 39.1.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

27/07/98

International application No.

PCT/SE 98/00907

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9511891 A1	04/05/95	AU 687115 B	19/02/98
		AU 8069794 A	22/05/95
		BR 9407910 A	26/11/96
		CA 2173257 A	04/05/95
		CN 1136811 A	27/11/96
		CZ 9601114 A	11/09/96
		EP 0725779 A	14/08/96
		FI 961809 A	20/05/96
		HR 940890 A	31/12/96
		HU 75060 A	28/03/97
		HU 9601103 D	00/00/00
		IL 111365 D	00/00/00
		JP 9504287 T	28/04/97
		NO 961687 A	03/06/96
		PL 314086 A	19/08/96
		SK 43696 A	01/10/96
		US 5420151 A	30/05/95
		US 5500425 A	19/03/96
		US 5616610 A	01/04/97
		US 5639772 A	17/06/97
		US 5639784 A	17/06/97
		US 5641807 A	24/06/97
		US 5646309 A	08/07/97
		US 5650524 A	22/07/97
		US 5656657 A	12/08/97
		US 5656658 A	12/08/97
		ZA 9408353 A	02/05/95

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